UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 30, 2003

MEMORANDUM:

Subject: Ethylene Thiourea
DP Barcode: D289726
Case No.: 0643

From: Marianne Lewis, Biologist
Product Reregistration Branch
Special Review and Reregistration Division (7508C)

To: Ann Overstreet, CRM
RBIII
Special Review and Reregistration Division (7508C)

Applicant: EBDC/ETU Task Force
600 13th Street, N.W.
Suite 1200
Washington, D.C. 20005-3096

FORMULATION:

% by wt.

Active Ingredient(s):
Ethylene thiourea:
.....

..... 99.6%
Inert Ingredient(s):
.....
..... 0.4% Total
100.0%

BACKGROUND: The EBDC/ETU Task Force has submitted four acute toxicity studies for review. The MRID's are as follows: 458881-01 (81-2), 458881-02 (81-3), 458881-04 (81-4), and
458881-03 (81-5). The studies were conducted by LPT Laboratory or Pharmacology and Toxicology KG and the test material used in each of the studies was 99.6% Ethylene thiourea, a light beige powder.

RECOMMENDATIONS:

- Three (81-2, 81-3, 81-5) of the four studies submitted are acceptable.
- The primary eye irritation study (81-4) is unacceptable. However, based on the information contained in the study and found in the open literature the Agency will classify the subject product as a Toxicity Category IV for this acute toxicity requirement. A new study is not needed.

Procedural Deviations:

Acute Dermal Study (81-2): The laboratory suspended the test material in sesame oil without justifying the selection of this vehicle. If water or saline cannot be utilized other vehicles may be used as long as the replacement vehicle is non-toxic, non-irritating, and will not substantially change the properties of the test material. Also, the effect the vehicle has on the permeability of the test substance should be taken into consideration. The inability to use water or saline should be justified in the report.

Primary Eye Irritation Study (81-4): The laboratory conducted sodium fluorescein staining at 24 hours. Although the Agency strongly encourages the use of sodium fluorescein staining, the Agency agrees that it is an optional tool that the laboratory can use in detecting cornea epithelial damage. However, if it is not done correctly it is not acceptable. Sodium fluorescein is a weak organic acid and it is very efficient in absorbing ultraviolet light and emitting fluorescent lights. The maximum absorption for this stain is

490µm (excitation) and its maximum emission is 520µm. Because this stain is highly fluorescent it can be detected at very low concentrations using UV light in biologic tissues & fluids. A regular incandescent light bulb would be inadequate to detect the majority of the staining. If the laboratory is going to conduct the sodium fluorescent staining, the correct protocol should be followed. This study is unacceptable. However, based on the information available in the study and the open literature the Agency will classify this product as Toxicity Category IV. A new study is not needed.

The acute toxicity profile for 99.6% Ethylene thiourea is currently:

Acute Oral		Data Needed
Acute Dermal		III
		Acceptable
Acute Inhalation	IV	Acceptable
Primary Eye	IV	Unacceptable
Primary Dermal	IV	Acceptable
Skin Sensitization		Data Needed

DATA REVIEW FOR ACUTE DERMAL TOXICITY (§81-2, 870.1100)

Product Manager: Mary Waller, 21 **Reviewer:** Marianne Lewis
MRID No.: 458881-01 **Study Completion Date:** 3/6/03
Report No.: 13986/01

Testing Laboratory: LPT Laboratory of Pharmacology & Toxicology KG
Author: P.Leuschner

Quality Assurance (40 CFR § 160.12): Included

Test Material: Ethylene Thiourea, light beige powder, 99.6%

Species: Sprague-Dawley Crl:CD BR
Weight: males = 203 - 235 g ; females = 208 - 227 g
Age: young adult
Source: Charles River Deutschland GmbH

Summary:

1. **LD_{50} (mg/kg):** > 2000 mg/kg

2. **Tox. Category:** III **Classification:** Acceptable

Procedure (Deviations From §81-2):

- the test material was suspended in sesame oil without any justification for this vehicle

Results: **Reported Mortality**

DOSAGE (mg/kg)	(number deaths/number tested)		
	Males	Females	Combined
2000	0/5	0/5	0/10

Observations: Twenty four hours prior to application, the back of each test animal was clipped free of hair exposing an area of 5 x 6 cm (approx. 10% of the total body surface). The test material was applied to the intact test sites and covered with 8 layers of gauze. The gauze was then covered with a

plastic sheet and secured with adhesive tape. After 24 hours, the gauze and plastic sheets were removed and any residual substance was removed.

No abnormal clinical signs were noted.

Gross Necropsy Findings: No observable abnormalities were noted.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3, 870.1300)

Product Manager: Mary Waller, 21 **Reviewer:** Marianne Lewis
MRID No.: 458881-02 **Study Completion Date:** 3/6/03
Report No.: 15283/02

Testing Laboratory: LPT Laboratory of Pharmacology & Toxicology KG
Author: P.Leuschner

Quality Assurance (40 CFR § 160.12): Included

Test Material: Ethylene Thiourea, light beige powder, 99.6%

Species: Sprague-Dawley Crl:CD BR rat
Weight: males = 237 - 252 g; females = 202 - 211 g
Age: young adult
Source: Charles River Deutschland GmbH

Summary:

1. **LC_{50} (mg/L):** > 10.4 mg/L

2. **MMAD:** 2.065 µm **GSD:** 3.351

3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (Deviation From §81-3): none

Results: **Reported Mortality**

Exposure Concentration	(Number Deaths/Number Tested)		
	Males	Females	Combined
10.4 mg/L	0/5	0/5	0/10

Chamber Environment	Dose levels
	10.40 mg/L
Chamber Volume	40 L
Airflow	15 Lpm
Temperature (°C)	20.3 - 20.8
Relative Humidity (%)	46.5 - 47.5

Clinical Observations: Clinical signs observed: 10/10 reduced motility, 10/10 ataxia, 10/10 reduced muscle tone, & 10/10 dyspnoea. All signs cleared within the first 24 hours of exposure.

Gross Necropsy Findings: No abnormal observations were noted.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (§81-4, 870.2400)

Product Manager: Mary Waller, 21 **Reviewer:** Marianne Lewis
MRID No.: 458881-04 **Study Completion Date:** 3/6/03
Report No.: 13988/01

Testing Laboratory: LPT Laboratory of Pharmacology & Toxicology KG
Author: P.Leuschner

Quality Assurance (40 CFR § 160.12): Included

Test Material: Ethylene Thiourea, light beige powder, 99.6%

Dosage: 100 mg
Species: Himalayan rabbit
Sex: 3 males
Weight: 2.2 - 2.3 kg (individual weights not stated)

Age: 7 - 8 months
Source: LPT breeding colony

Summary:

Classification: Unacceptable

Procedure (Deviations From §81-4):

· lab did not utilize a UV light during sodium fluorescein method.

Results:

OBSERVATIONS	(number "positive"/number tested)			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iris	0/3	0/3	0/3	0/3

Conjunctivae				
Redness	0/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3
Discharge	0/3	0/3	0/3	0/3

No irritation/opacity was seen in any of the test animals during the study.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5, 870.2500)

Product Manager: Mary Waller, 21 **Reviewer:** Marianne Lewis
MRID No.: 458881-03 **Study Completion Date:** 3/6/03
Report No.: 13987/01

Testing Laboratory: LPT Laboratory of Pharmacology & Toxicology KG
Author: P.Leuschner

Quality Assurance (40 CFR § 160.12): Included

Test Material: Ethylene Thiourea, light beige powder, 99.6%

Dosage: 500 mg moistened with distilled water
Species: Himalayan rabbit
Age: 5 - 6 months
Sex: 3 males
Weight: 2.2 - 2.5 kg
Source: LPT breeding colony

Summary:

1. **Toxicity Category:** IV

2. **Classification:** Acceptable

Procedure (Deviations From §81-5): none

Results: Twenty four hours prior to application of the test material, the fur was shaved from the dorsal area of the trunk of each test animal. The test material was moistened and applied to the intact test site (approx. 6 cm^2). The test material was then covered with a gauze patch which was held in place with non-irritating tape. After the four hour exposure the patches were removed and the test sites evaluated.

No dermal irritation was noted at any of the test sites during the study.

ACUTE TOX ONE-LINER

1. PC CODE: 014504

2. CURRENT DATE: April 30, 2003

3. TEST MATERIAL: Ethylene Thiourea, light beige powder, 99.6%

Study/Species/ Lab/Study#/Date	MRID #	Results	Tox. Cat.	Core Grade
acute dermal toxicity/rat/LPT/ 13986/01/03-06-03	45888101	LD_{50} > 2000 mg/kg	III	A
acute inhalation toxicity/rat/ LPT/15283/02/03-06-03	45888102	LC_{50} >10.4 mg/L MMAD = 2.065 μm; GSD = 3.351		A
primary eye irritation/rabbit/ LPT/13988/01/03-06-03	45888104			U
primary dermal irritation/ rabbit/LPT/13987/01/03-06-03	45888103	No dermal irritation was noted at any of the test sites during the study.	IV	A

Core Grade Key:
A = Acceptable
S = Supplementary (upgradeable)
U = Unacceptable
V = self-Validated